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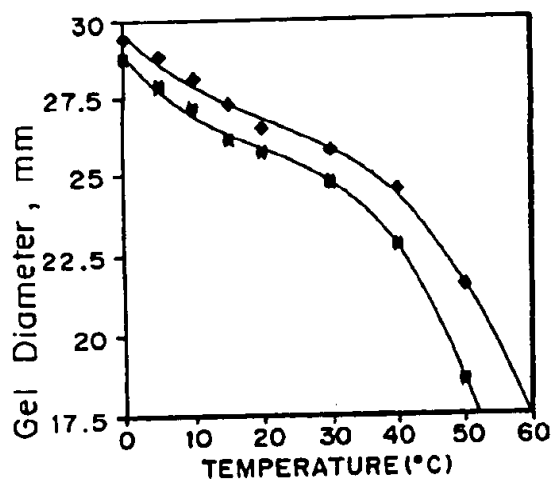
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(21) International Application Number: PCT/US96/12285 (22) International Filing Date: 26 July 1996 (26.07.96) (30) Priority Data: 60/001,723 28 July 1995 (28.07.95) US (71) Applicant: FOCAL, INC. [US/US]; 4 Maguire Road, Lexington, MA 02173 (US). (72) Inventors: PATHAK, Chandrashekhar, P.; 314 Bedford Street #105, Lexington, MA 02173 (US). BARMAN, Shikha, P.; 61 East Meadow Lane #19, Lowell, MA 01854 (US). PHILBROOK, C., Michael; 199 Marlborough Street #301, Boston, MA 02116 (US). SAWHNEY, Amarpreet; 2 Opi Circle, Lexington, MA 02173 (US). COURY, Arthur, J.; 154 Warren Avenue, Boston, MA 02116 (US). AVILA, Luis, Z.; 23 Rockaway Lane, Arlington, MA 02174 (US). KIERAS, Mark, T.; 23 Purchase Street, Newburyport, MA 01950 (US). (74) Agent: PABST, Patrea, L.; Arnall Golden & Gregory, 2800 One Atlantic Center, 1201 West Peachtree Street, Atlanta, GA 30309-3450 (US).		(81) Designated States: CA, JP, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report With amended claims. (88) Date of publication of the international search report: 13 March 1997 (13.03.97) Date of publication of the amended claims: 15 May 1997 (15.05.97)	

(54) Title: MULTIBLOCK BIODEGRADABLE HYDROGELS FOR USE AS CONTROLLED RELEASE AGENTS FOR DRUGS DELIVERY AND TISSUE TREATMENT AGENTS



- ◆ PEO-PPO-PEO
CO-POLY(LACTATE)
ACRYLATE
- PEO-PPO-PEO
CO-POLY(CAPROATE)
ACRYLATE

(57) Abstract

Gel-forming macromers including at least four polymeric blocks, at least two of which are hydrophobic and at least one of which is hydrophilic, and including a cross-linkable group are provided. The macromers can be covalently cross-linked to form a gel on a tissue surface *in vivo*. The gels formed from the macromers have a combination of properties including thermosensitivity and lipophilicity, and are useful in a variety of medical applications including drug delivery and tissue coating.

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AMENDED CLAIMS

[received by the International Bureau on 4 April 1997 (04.04.97);
original claims 1-50 replaced by amended claims 1-37 (5 pages)]

1. A macromer comprising at least four covalently linked polymeric blocks and at least one crosslinkable group, wherein
 - a) at least one block is hydrophilic
 - b) each hydrophilic block individually has a water solubility of at least 1 gram/liter; and
 - c) at least two blocks are sufficiently hydrophobic to aggregate to form micelles in an aqueous continuous phase,wherein the macromer is capable of being reversibly gelled or crosslinked in solution in response to a change in temperature, ionic concentration or pH, and
wherein the crosslinkable group is selected from the group consisting of epoxides, isocyanates, isothiocyanates, aldehydes, amines, sulfonic acids, carboxylic acids and ethylenically unsaturated groups.
2. The macromer of claim 1 wherein the hydrophilic blocks are the same or different and are selected from the group consisting of poly(ethylene glycol), poly(ethylene oxide), poly(vinyl alcohol), poly(vinylpyrrolidone), poly(ethyloxazoline), polysaccharides and amino acid polymers.
3. The macromer of claim 1 wherein the hydrophobic blocks are the same or different and are selected from the group consisting of polypropylene oxide, polybutylene oxide, hydrophobic mixed poly(alkylene oxides), polyhydroxy acids, polylactones, polyamino acids, polyanhydrides, polyorthoesters, polyphosphazenes, and polyphosphates.
4. The macromer of claim 1 wherein the crosslinkable group is selected from the group consisting of epoxides, isocyanates, isothiocyanates, aldehydes, amines, sulfonic acids and carboxylic acids.
5. The macromer of claim 1 wherein the crosslinkable groups comprise ethylenically unsaturated groups.

6. The macromer of claim 1, further comprising at least one ionically charged moiety covalently attached to the macromer.

7. The macromer of claim 1 comprising at least two chemically distinct hydrophobic blocks.

8. The macromer of claim 1 wherein the crosslinkable groups are separated by at least one hydrophobic block, wherein the hydrophobic block is capable of degrading under physiological conditions.

9. The macromer of claim 1 wherein at least one hydrophobic block is separated from any crosslinkable group by at least one hydrophilic block.

10. The macromer of claim 1 wherein each hydrophobic block is separated from any other hydrophobic block by a hydrophilic block.

11. The macromer of claim 1 wherein the macromer comprises at least one thermally sensitive region, and wherein a solution of the macromer is capable of gelling or crosslinking to produce a hydrogel with a temperature dependent volume.

12. The macromer of claim 1 wherein the macromer is capable of thermoreversible gelation in an aqueous solution of the macromer at a concentration of at least 2% by weight, and wherein the gelation temperature is between about 0°C and about 65°C.

13. A composition comprising a macromer as described in claim 1 and a therapeutic agent.

14. A composition comprising a macromer as described in claim 1 and a hydrophobic material non-covalently associated with the macromer.

15. The composition of claim 14, wherein the hydrophobic material is selected from the group consisting of a hydrocarbon, a lipid, a fatty acid, and a sterol.

16. A composition including a macromer as described in claim 1 and a pharmaceutically acceptable carrier.

17. The composition of claim 16 wherein the carrier is suitable for parenteral administration.

18. The composition of claim 16, wherein the macromer is gelled.

19. The composition of claim 16, wherein the crosslinkable groups on the macromer are covalently crosslinked.

20. The composition of claim 19 further comprising a therapeutic agent.

21. The composition of claim 20, wherein the therapeutic agent is provided in a form selected from the group consisting of particles, microparticles, pro-drug conjugates, or liposomes.

22. The composition of claim 19 wherein the gel is formed on a surface of biological tissue.

23. The composition of claim 19 wherein the gel is formed on a surface of a medical device.

24. The composition of claim 19 wherein the gel is formed between opposed surfaces, tending thereby to adhere said surfaces.

25. Use of a macromer as described in claim 1 to prepare a composition for treating a medical condition by applying an aqueous solution of the macromer to tissue *in vivo*.

26. The use of claim 25 wherein the aqueous solution further comprises a dissolved or suspended therapeutic agent.

27. The use of claim 25 wherein the medical condition is a burn or abrasion of the skin.

28. The use of claim 25 wherein the medical condition is an injury resulting from a surgical intervention.

29. The use of claim 28 wherein the surgery is angioplasty.

30. The use of claim 28 wherein the surgery is conducted through the cannula of a trocar.

31. A method for controlling the rate of delivery of a biologically active material, comprising:

- a) mixing an active material with a solution of a macromer as described in claim 1;
- b) crosslinking the macromer to form a gel; and
- c) changing the permeability of the gel to effect controlled delivery of the material.

32. The method of claim 31 wherein the crosslinked gel changes in permeability in response to an effect selected from the group consisting of a change in temperature, a change in ionic concentration, and a change in pH.

33. The method of claim 31 wherein at least one hydrophobic block aggregates in aqueous solution to form a hydrophobic domain.

34. The method of claim 33 wherein the hydrophobicity of said domain is controlled by selecting the hydrophobicity of the block.

35. The method of claim 40 wherein the hydrophobicity of said domain is controlled by adding hydrophobic materials to the gel-forming macromer solution.

36. The method of claim 31 wherein the active material is in the form selected from the group consisting of particles, microparticles, pro-drug conjugates, and liposomes.

37. The method of claim 36 wherein the crosslinked gel forms a microparticle after crosslinking.